ANNALS of Clinical and Translational Neurology
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AMERICAN NEUROLOGICAL ASSOCIATION

REPLY TO LETTER

Reply to: "Inappropriate interpretation of non-pathogenic *HTRA1* variant as pathogenic"

Chen Zhang[1,2], Honghua Zheng[3], Xin Li[3], Shaowu Li[4], Wei Li[2,5], Ziwei Wang[3], Songtao Niu[1,2], Xingao Wang[1,2] & Zaiqiang Zhang[1,2]

[1]Department of Neurology, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
[2]National Clinical Research Center for Neurological Diseases, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
[3]Fujian Provincial Key Laboratory of Neurodegenerative Disease and Aging Research, Institute of Neuroscience, School of Medicine, Xiamen University, Fujian,Xiamen, China
[4]Beijing Neurosurgical Institute, Beijing Tiantan Hospital, Capital Medical University, Beijing, China
[5]Monogenic Disease Research Center for Neurological Disorders, Beijing Tiantan Hospital, Capital Medical University, Beijing, China

Dear Editor,

We thank Uemura et al.[1] for their letter suggesting interpreting the *HTRA1* A20V variant as non-pathogenic.

It is true that the *HTRA1* A20V variant had a higher frequency of carriers compared with the other pathogenic *HTRA1* variants identified in our study. However, it must be noted that all carriers with *HTRA1* A20V variants in our study had clinical phenotypes that were consistent with *HTRA1*-related cerebral small vessel disease. Moreover, carriers with both homozygous and heterozygous *HTRA1* A20V variants were affected, and family members without this variant were not affected.[2]

Many of the pathogenic *HTRA1* variants reported to date are positioned within domains known to affect enzymatic function. The p.A20V (c.59C>T) variant is positioned within HTRA1's N-terminal domain, the function(s) of which remain largely unknown.[3] It does bear mention that a study reported autolysis of the N-terminal domain does not affect protease activity.[4] Functional investigations into the pathophysiological impacts of the p.A20V (c.59C>T) variant will be necessary to better understand its role in the development of cerebral small vessel disease.

Funding Information

This study was supported by a grant from the Beijing Municipal Science and Technology Commission (No. Z171100001017080).

Conflict of Interest

None.

References

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